

09/02/2004

L11 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:676651 CAPLUS
DOCUMENT NUMBER: 139:320606
TITLE: Specific amino-acid residues in the N-terminus and TM3
implicated in channel function and oligomerization
compatibility of **connexin43**
AUTHOR(S): Lagree, Valerie; Brunschwig, Karin; Lopez, Patricia;
Gilula, Norton B.; Richard, Gabriele; Falk, Matthias
M.
CORPORATE SOURCE: Department of Cell Biology, The Scripps Research
Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of Cell Science (2003), 116(15), 3189-3201
CODEN: JNCSAI; ISSN: 0021-9533
PUBLISHER: Company of Biologists Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To identify signals that convey **connexin** oligomerization
compatibility, we have aligned amino-acid sequences of .alpha. and .beta.
group **connexins** (Cx) and compared the physicochem. properties of
each homologous amino-acid residue. Four positions were identified that
consistently differed between .alpha. and .beta.-type **connexins**;
two are located in the N-terminal domain (P1 and P2, corresponding to
residues 12 and 13 of the Cx43 sequence), and two in the third
trans-membrane-spanning domain TM3 (P3 and P4, corresponding to residues
152 and 153 of the Cx43 sequence). Replacement of each of these residues
in Cx43 (an .alpha.-type **connexin**) with the corresponding
residues of Cx32 (a .beta.-type **connexin**) resulted in the
assembly of all **variants** into **gap junctions**;
however, only the P4 **variant** was functional, as indicated by
lucifer yellow dye transfer assays. The other three variants exerted a
moderate to severe dose-dependent, dominant-neg. effect on co-expressed
wild-type (wt) Cx43 channel activity. Moreover, a significant
dose-dependent, trans-dominant inhibition of channel activity was obsd.
when either one of the N-terminal variants was co-expressed with wt Cx32.
Assembly analyses indicated that dominant and trans-dominant inhibitory
effects appeared to be based on the oligomerization of wt and
variant connexins into mixed connexons. Interestingly,
the identified N-terminal amino acids coincide with the position of
naturally occurring, disease-causing missense mutations of several .beta.-
connexin genes (Cx26, Cx30, Cx31, Cx32). Our results demonstrate
that three of the identified discriminative amino-acid residues (positions
12, 13 and 152) are crucial for Cx43 channel function and suggest that the
N-terminal amino-acid residues at position 12/13 are involved in the
oligomerization compatibility of .alpha. and .beta. **connexins**.

REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 5 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

ACCESSION NUMBER: 2003:1049795 SCISEARCH
THE GENUINE ARTICLE: 747CH
TITLE: The role of **connexins** in human disease
AUTHOR: Chang E H; Van Camp G; Smith R J H (Reprint)
CORPORATE SOURCE: Univ Iowa, Dept Otolaryngol Head & Neck Surg, Mol
Otolaryngol Res Labs, 200 Hawkins Dr, Iowa City, IA 52242
USA (Reprint); Univ Iowa, Dept Otolaryngol Head & Neck
Surg, Mol Otolaryngol Res Labs, Iowa City, IA 52242 USA;
Univ Antwerp, Dept Med Genet, B-2020 Antwerp, Belgium
COUNTRY OF AUTHOR: USA; Belgium

09/02/2004

SOURCE: EAR AND HEARING, (AUG 2003) Vol. 24, No. 4, pp. 314-323.
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST,
PHILADELPHIA, PA 19106-3621 USA.
ISSN: 0196-0202.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 66

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Connexins** are the building blocks of **gap junctions**. In forming a **gap junction**, six **connexins** oligomerize to form a hexameric torus called a **connexon**. The number of **gap junctions** in a cell ranges from a few to over 10(5) and imparts to interconnected cells a uniform phenotype. The crucial role that **gap junctions** play in normal physiology is reflected by the diverse spectrum of human diseases in which allele **variants** of different **gap junction** genes are implicated. In particular, mutations in GJB2 are a major cause of autosomal recessive non-syndromic deafness. This discovery has impacted medical practice and makes it incumbent on clinicians to familiarize themselves with the genetic advances that are rapidly occurring in our field.

L11 ANSWER 3 OF 5 MEDLINE on STN DUPLICATE 1

ACCESSION NUMBER: 2002307681 MEDLINE

DOCUMENT NUMBER: 22013902 PubMed ID: 12019212

TITLE: A mutation in GJB3 is associated with recessive erythrokeratoderma variabilis (EKV) and leads to defective trafficking of the **connexin** 31 protein.

AUTHOR: Gottfried Irit; Landau Marina; Glaser Fabian; Di Wei-Li; Ophir Joseph; Mevorah Barukh; Ben-Tal Nir; Kelsell David P; Avraham Karen B

CORPORATE SOURCE: Department of Human Genetics and Molecular Medicine, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel.

SOURCE: HUMAN MOLECULAR GENETICS, (2002 May 15) 11 (11) 1311-6.
Journal code: 9208958. ISSN: 0964-6906.

PUB. COUNTRY: England; United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200210

ENTRY DATE: Entered STN: 20020611

Last Updated on STN: 20021011

Entered Medline: 20021010

AB Erythrokeratoderma variabilis (EKV) is a skin disorder characterized by variable (transient) erythemas and fixed keratosis. The disorder maps to chromosome 1p34-35, a location that contains the GJB3 gene encoding the **gap junction** protein **connexin** 31. Until now, only heterozygote mutations in the form of dominant inheritance have been described in this gene associated with EKV. We report here a homozygote mutation in the **connexin** 31 gene, found in a family that shows recessive inheritance of the disorder, thus providing the first molecular support for a recessive **variant** of EKV. The entire GJB3 coding sequence was scanned for mutations by sequencing. We detected a T-->C transition at position 101 of the coding sequence, which replaces a leucine with a proline at residue 34 of the protein (L34P). Evolutionary analysis shows that this mutation is located at a highly conserved region of **connexin** in the first putative transmembrane helix (TMH). In

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transfected keratinocytes, L34P **connexin** 31 had a cytoplasmic distribution, suggesting that the mutant form of this protein will not form normal **gap junctions** between adjacent cells. The change of leucine to proline is likely to alter the structure of the first TMH of **connexin** by inducing a kink, thus influencing **connexon** structure and function.

L11 ANSWER 4 OF 5 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2000448478 MEDLINE
DOCUMENT NUMBER: 20455131 PubMed ID: 11001493
TITLE: Biosynthesis and structural composition of **gap junction** intercellular membrane channels.
AUTHOR: Falk M M
CORPORATE SOURCE: Department of Cell Biology, The Scripps Research Institute, La Jolla, CA 92037, USA.. mfalk@scripps.edu
SOURCE: EUROPEAN JOURNAL OF CELL BIOLOGY, (2000 Aug) 79 (8) 564-74. Ref: 91
Journal code: 7906240. ISSN: 0171-9335.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010118

AB **Gap junction** channels assemble as dodecameric complexes, in which a hexameric **connexon** (hemichannel) in one plasma membrane docks end-to-end with a **connexon** in the membrane of a closely apposed cell to provide direct cell-to-cell communication. Synthesis, assembly, and trafficking of the **gap junction** channel subunit proteins referred to as **connexins**, largely appear to follow the general secretory pathway for membrane proteins. The **connexin** subunits can assemble into homo-, as well as distinct hetero-oligomeric connexons. Assembly appears to be based on specific signals located within the **connexin** polypeptides. Plaque formation by the clustering of **gap junction** channels in the plane of the membrane, as well as channel degradation are poorly understood processes that are topics of current research. Recently, we tagged **connexins** with the autofluorescent reporter green fluorescent protein (GFP), and its cyan (CFP), and yellow (YFP) color **variants** and combined this reporter technology with single, and dual-color, high resolution deconvolution microscopy, computational volume rendering, and time-lapse microscopy to examine the detailed organization, structural composition, and dynamics of **gap junctions** in live cells. This technology provided for the first time a realistic, three-dimensional impression of **gap junctions** as they appear in the plasma membranes of adjoining cells, and revealed an excitingly detailed structural organization of **gap junctions** never seen before in live cells. Here, I summarize recent progress in areas encompassing the synthesis, assembly and structural composition of **gap junctions** with a special emphasis on the recent results we obtained using cell-free translation/membrane-protein translocation, and autofluorescent reporters in combination with live-cell deconvolution microscopy.

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L11 ANSWER 5 OF 5 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2001180578 MEDLINE
DOCUMENT NUMBER: 21084473 PubMed ID: 11216656
TITLE: The M34T allele **variant** of **connexin** 26.
AUTHOR: Cucci R A; Prasad S; Kelley P M; Green G E; Storm K;
Willocx S; Cohn E S; Van Camp G; Smith R J
CORPORATE SOURCE: Department of Otolaryngology, Head and Neck Surgery, Iowa
City, IA 52242, USA.
CONTRACT NUMBER: R01-DC02842 (NIDCD)
SOURCE: GENETIC TESTING, (2000) 4 (4) 335-44.
Journal code: 9802546. ISSN: 1090-6576.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010329

AB GJB2 encodes the protein **Connexin** 26, one of the building blocks
of **gap junctions**. Each **Connexin** 26 molecule
can oligomerize with five other **connexins** to form a
connexon; two connexons, in turn, can form a **gap**
junction. Because mutations in GJB2 are the most common cause of
congenital severe-to-profound autosomal recessive nonsyndromic hearing
loss, the effect of the **Connexin** 26 allele **variants** on
this dynamic 'construction' process and the function of any **gap**
junctions that do form is particularly germane. One of the more
controversial allele variants, M34T, has been hypothesized to cause
autosomal dominant nonsyndromic hearing loss. In this paper, we present
clinical and genotypic data that refutes this hypothesis and suggests that
the effect of the M34T allele variant may be dependent on the mutations
segregating in the opposing allele.

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(FILE 'HOME' ENTERED AT 14:59:20 ON 09 FEB 2004)

FILE 'MEDLINE, CAPLUS, SCISEARCH, BIOSIS' ENTERED AT 14:59:34 ON 09 FEB
2004

L1 16918 S CONNEXIN?
L2 1853 S L1(S) (ACTIVITY OR FUNCTION)
L3 17 S L2(P)VARIANT
L4 5 DUP REM L3 (12 DUPLICATES REMOVED)
L5 5 S L2(S)VARIANT
L6 5 DUP REM L5 (0 DUPLICATES REMOVED)
L7 4 S L6 NOT L4
L8 336 S L1 AND CONNEXON
L9 322 S L8 AND GAP(W)JUNCTION?
L10 13 S L9 AND (CONNEXIN?(S)VARIANT?)
L11 5 DUP REM L10 (8 DUPLICATES REMOVED)